

US007427605B2

(12) United States Patent

Davis et al.

(54) INHIBITORS OF RIBONUCLEOTIDE REDUCTASE SUBUNIT 2 AND USES THEREOF

(75) Inventors: Mark E. Davis, Pasadena, CA (US);

Jeremy D. Heidel, Pasadena, CA (US); John J. Rossi, Altaloma, CA (US)

(73) Assignee: Calando Pharmaceuticals, Inc.,

Pasadena, CA (US)

(*) Notice: Subject to any disclaimer, the term of this

patent is extended or adjusted under 35

U.S.C. 154(b) by 68 days.

(21) Appl. No.: 11/396,365

(22) Filed: Mar. 31, 2006

(65) Prior Publication Data

US 2006/0263435 A1 Nov. 23, 2006

Related U.S. Application Data

- (60) Provisional application No. 60/742,100, filed on Dec. 2, 2005, provisional application No. 60/695,931, filed on Jun. 30, 2005, provisional application No. 60/667, 362, filed on Mar. 31, 2005.
- (51) Int. Cl. A61K 31/70 (2006.01) A61K 31/715 (2006.01) C07H 21/04 (2006.01)
- (52) **U.S. Cl.** **514/44**; 536/24.5; 514/58

(56) References Cited

U.S. PATENT DOCUMENTS

4,945,195	\mathbf{A}		7/1990	Ipcinski	
5,998,383	A	*	12/1999	Wright et al.	 514/44

(10) Patent No.:

US 7,427,605 B2

(45) **Date of Patent:**

Sep. 23, 2008

6,030,942	A	2/2000	Cooperman et al.	
7,056,704	B2*	6/2006	Tuschl et al	435/91.1
7.098.030	B2 *	8/2006	Rozema et al	514/44

FOREIGN PATENT DOCUMENTS

WO WO02/24864 3/2002

OTHER PUBLICATIONS

Cerqueria et al., 2005, Overview of ribonucleotide reductase inhibitors: an appealing target in anti-tumour therapy, Curr. Med. Chem. 12:1283

Database EMBL, Aug. 12, 2002, XP0024007222, database accession No. BQ670934.

Duxbury et al., 2004, Retrovirally mediated RNA interference targeting the M2 subunit of ribonucleotide reductase: A novel therapeutic strategy in pancreatic cancer, Surgery 136:261-269.

Duxbury et al., 2004, RNA interference targeting the M2 subunit of ribonucleotide reductase enhances pancreatic adenocarcinoma chemosensitivity to gemcitabine, Oncogene 28:1539-1548.

Kim et al., 2002, Database EMBL, XP002407223, Database accession No. BM754277.

Kittler et al., 2004, An endoribonuclease-prepared siRNA screen in human cells identifies genes essential for cell division, Nature 432:1036-1040.

Lin et al., 2004, Stable suppression of the R2 subunit of ribonucleotide reductase by R2-targeted short interference RNA sensitizes p53(-/-) HCT-116 colon cancer cells to DNA-damaging agents and ribonucleotide reductase inhibitors, J. Biol. Chem. 279:27030. Zhou et al., 2003, The human ribonucleotide reductase subunit hRRM2 complements p53R2 in response to UV-induced DNA repair in cells with mutant p53, Cancer Res. 63:6583-6594.

* cited by examiner

Primary Examiner—Richard Schnizer (74) Attorney, Agent, or Firm—Ropes & Gray LLP

(57) ABSTRACT

The present application relates to inhibitors of ribonucleotide reductase subunit 2 (R2), and methods and compositions related to the R2 inhibitors. In certain embodiments, the R2 inhibitors include nucleic acids, such as for example siRNAs.

14 Claims, 45 Drawing Sheets